PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
O'BRIEN, Caroline, J.
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
ROYAUME-UNI

10 SEP 1999

Date of mailing (day/month/year) 02 September 1999 (02.09.99)	
Applicant's or agent's file reference COB/BP5760178	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/GB99/00583	26 February 1999 (26.02.99)	26 February 1998 (26.02.98)

Applicant
CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,EP,IL,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,
   ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,
   SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   02 September 1999 (02.09.99) under No. WO 99/43801

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switz rland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 04 November 1999 (04.11.99)	
International application No. PCT/GB99/00583	***Applicant's or agent's file reference*** COB/BP5760178
International filing date (day/month/year) 26 February 1999 (26.02.99)	**Priority date** (day/month/year) 26 February 1998 (26.02.98)
Applicant DURRANT, Linda, Gillian et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

23 September 1999 (23.09.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 *Geneva 20, Switzerland*

Facsimile No.: (41-22) 740.14.35

Authorized officer

Juan Cruz

Telephone No.: (41-22) 338.83.38

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
COB/BP5760178		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/00583	26/02/1999	26/02/1998
Applicant		
CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [X] furnished subsequently to this Authority in written form.

   [X] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   ANTI-ANGIOGENIC VACCINES: SUBSTANCES AND METHODS RELATING THERETO

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/00583

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 41-43
are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/00583

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/71 A61K38/17 A61K39/00 G01N33/50
G01N33/68 C12Q1/68 C07K16/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K A61K G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 21866 A (LUDWIG INSTITUTE FOR CANCER RES (US); RUNTING AS; WILKS AF; STACKER SA) 17 August 1995 see page 21, line 18 - page 22, line 21	1-5, 12-30, 33-40
X	WO 94 00469 A (IMMUNEX CORPORATION (US); ZIEGLER S.F.) 6 January 1994 see page 9, line 19-24 see page 26, line 4-37; example 4 Seq.ID:2 see page 34 - page 37	1-5, 12-30, 33-40

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 June 1999	02/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Macchia, G

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Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/GB 99/00583

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 681 714 A (MOUNT SINAI HOSPITAL CORP (CA); BREITMAN; ROSSANT; DUMONT; YAMAGUCHI) 28 October 1997 see column 18, line 3-53 see column 23, line 44-67 see column 34, line 24-38	1-5, 12-30, 33-40
X	WO 95 13387 A (MAX-PLANCK-GESELLSCHAFT ZUR FÖRDERUNG DER WISSENSCHAFTEN EV (DE) RISAU) 18 May 1995 see page 27, line 32 - page 29, line 33	1-5, 12-30, 33-40
A	D'AMARO J. ET AL.: "A computer program for predicting possible cytotoxic T lymphocytes epitopes based on HLA class I peptide-binding motifs" HUMAN IMMUNOLOGY, vol. 43, no. 1, 1 May 1995, pages 13-18, XP002015451 see abstract	
A	DAVENPORT M.P. ET AL.: "An empirical method for the prediction of T-cell epitopes" IMMUNOGENETICS, vol. 42, no. 5, 1 January 1995, pages 392-397, XP002015224 see abstract	
A	WO 97 41440 A (UNIV LEIDEN; SEED CAPITAL INVESTMENTS (SCI) BV (NL) VAN DER BURG ET AL) 6 November 1997 see abstract	
A	RESSING M.E. ET AL.: "Immunotherapy of cancer by peptide-based vaccines for the induction of tumor-specific T cell immunity" IMMUNOTECHNOLOGY, vol. 2, no. 4, 1 November 1996, page 241-251 XP004063120 see abstract	

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Information on patent family members

International Application No
PCT/GB 99/00583

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9521866 A	17-08-1995	AU 1874595 A	29-08-1995
		CA 2182681 A	17-08-1995
		EP 0812332 A	17-12-1997
		JP 10503081 T	24-03-1998
WO 9400469 A	06-01-1994	AU 4651893 A	24-01-1994
		US 5447860 A	05-09-1995
US 5681714 A	28-10-1997	CA 2085291 A	31-01-1994
WO 9513387 A	18-05-1995	AU 8143094 A	29-05-1995
WO 9741440 A	06-11-1997	AU 2410697 A	19-11-1997
		EP 0900380 A	10-03-1999

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
COB/BP5760178		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/00583	26/02/1999	26/02/1998
International Patent Classification (IPC) or national classification and IPC		
C12N15/12		
Applicant		
CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/09/1999	05.06.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Julia, P Telephone No. +49 89 2399 8410

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/00583

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-38	as originally filed				
Claims, No.:					
1-5,6 (part),22 (part), 23-35	as originally filed				
6 (part),7-21,22 (part), 36-41	as received on	29/03/2000	with letter of	24/03/2000	
Drawings, sheets:					
1/7-7/7	as originally filed				

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-41
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-41
Industrial applicability (IA)	Yes:	Claims	1-38
	No:	Claims	39-41 (see Citations and explanations)

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. Additional remarks to item I :

A "Sequence Listing" has been filed with the present application. This "Sequence Listing" comprises SEQ ID No.: 1 to SEQ ID No.: 17 (pages 1-19).

2. Additional remarks to item II :

The priority documents pertaining to the present application were not available at the time of establishing this international preliminary examination report (IPER). Hence, the current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document (26.02.98).

3. Additional remarks to item V :

The present application discloses peptides/polypeptides derived from the native or wild-type Tek (Tie2) receptor (receptor tyrosine kinase, RTK), with potential T cell epitopes (i.e. with the ability to stimulate an immune response, helper and/or cytotoxic T cell response) and which bind to an MHC molecule. In particular, Figure 5 outlines five possible regions (Tek1 to Tek5) and Table 1 (page 31) discloses eleven peptides Z1-Z9 and Z11-Z12 derived from these regions showing binding to MHC (except for Z4 and very weak for Z8). For peptides Z1, Z3, Z7 and Z32 (which encompasses both Z1 and Z3) it is shown a proliferation response of human T cells in vivo. The application explicitly claims these peptides/polypeptides (variants, equivalents, fragments, etc...), uses thereof, (mono and polyclonal) antibodies, nucleic acid thereof (recombinant, vector, plasmid, virus vector, host cell, method production, etc...), pharmaceutical compositions and therapeutic/prophylactic methods of treatment (reference is also made to use as cancer vaccines to direct an immune cell response to endothelial cells).

The arguments of the Applicant filed on 24.03.00 as a reply to the first written opinion have been duly taken into account but they have not been found to be relevant. The following documents have been cited in the International Search Report (ISR) as being relevant for assessing the novelty and inventiveness of the claimed subject matter:

i) WO-95/21866 (**D1**) discloses the production of a (recombinant) fusion protein comprising the extracellular domain of the Tek (tie2/Tek) receptor with a FLAG™ protein, alkaline phosphatase CAP or glutathione-S-transferase (GST) as a carrier. D1 further refers to the production of (mono and polyclonal) antibodies directed to said fusion protein (example 8). Pharmaceutical compositions comprising these antibodies and uses thereof are also

explicitly claimed. As far as the five regions identified in the present application, namely Tek1 to Tek5 are all located (55-90, 163-176, 345-362, 427-442 and 530-542) on the extracellular region of the Tek receptor (19-745), the IPEA considers that the molecule disclosed in D1 falls under the scope of claim 13, which certainly "**comprises** a peptide according to any one of claims 1 to 12 and one or more amino acid sequences not characteristics of Tek protein". The IPEA cannot agree with the Applicant in that the subject matter of claim 13 is restricted to the specific Tek1 to Tek5 peptides and due to the actual wording of claim 13, the IPEA maintains the objection raised in the written opinion. Thus, in agreement with the International Search Authority (ISA), the IPEA considers that all the embodiments of claims 14-30 and 33-38, concerned with subject-matter "dependent" formally or not on claim 13 (antibodies, nucleic acids, uses thereof, methods, etc...), are anticipated by the general and the specific teachings of D1 (Articles 33 (2) and (3) PCT.

In addition and in view of clarity problems (see "Additional remarks under item VIII", in particular paragraphs referring to : "peptide" defined by being "less than", "essentially", "a sequence which represents an epitope", etc...), the IPEA also considers that the molecule disclosed in D1 is "less than the full-length polypeptide sequence of native Tek" (it actually corresponds to the "Tek extracellular domain") and that it consists "essentially" of one or more amino acid sequences representing one or more epitopes of the Tek protein (in fact it comprises the five regions identified in the present application) and it can certainly bind (after partial cleavage?, see point (i.e) under "Additional remarks to item VIII" below) to an MHC molecule and stimulate an immune response as shown by the present application. Thus, the subject matter of claims 1-12 is anticipated by D1 as well (Articles 33 (2) and (3) PCT).

ii) WO-A-94/00469 (**D2**) discloses a receptor tyrosine kinase named ork which actually is the tie2/Tek receptor. Reference is made to the production of antigenic fragments and in particular there are several explicit references to the production of a soluble ork fragment comprising only the extracellular (ligand binding) domain of the ork receptor or parts thereof (page 4, lines 21-22; page 7, lines 28-35; page 8, lines 1-28; page 27 line 19, etc...) as well as to fusion products thereof (page 16) and the production of (specific) (mono and polyclonal) antibodies (example 4). D2 refers to the expression of the Tek receptor in endothelial cells (page 7 and example 3). In view of this disclosure and in agreement with the arguments given above for D1 (in particular due to the general and

ambiguous wording of the claims which are not clearly restricted to the specific "Tek epitopes" identified in the application), the IPEA considers that D2 anticipates the subject matter of claims 1-30 and 33-38 (Articles 33 (2) and (3) PCT).

iii) a similar disclosure is also found in the document US-A-5681714 (**D3**) which explicitly refers to generic fragments of the nucleic acid sequence encoding the Tek receptor of at least 18 bases (i.e. 6 residues) as well as generic peptide fragments of this receptor of at least 10 residues (column 12). Explicit mention is made of a fragment consisting of the extracellular domain of the Tek receptor and the production of general fusion proteins using the Tek receptor or said parts thereof (column 21). The document also discloses the expression of said receptor in endothelial cells (example VIII) and the use of the disclosed products for the production of antibodies and uses related to angiogenesis, cardiogenesis and tumorigenesis. In view of this disclosure and the arguments given above for D1-D2 (in particular due to the general and ambiguous wording of the claims which are not clearly restricted to the specific "Tek epitopes" identified in the application), the IPEA considers that the subject matter of claims 1-41 is anticipated by D3 (Articles 33 (2) and (3) PCT).

iv) WO-A-95/13387 (**D4**) refers too to soluble fragments derived from the Tek receptor. In particular for the production of antibodies (page 4, lines 1-5) or for screening peptide libraries for compounds binding to this soluble fragments (page 25, line 32 to page 26, line 4), wherein for this last application reference is also made to the production of "tag" or conjugate molecules. In agreement with the above argumentation, the disclosure of D4 anticipates at least the subject matter of claims 1-30 to 33-41 (Articles 33 (2) and (3) PCT).

v) J. D'Amaro et al., Human Immunol. 1995, Vol. 43, pages 13-18 (**D5**) discloses a computer program for predicting possible cytotoxic T lymphocyte epitopes based on HLA Class I peptide-binding motifs. The program predicted the presence of 27 peptides (of 9 residues each) in the early protein of human papillomavirus type 1a (HPV1a-E1) with the ability to bind MHC-I and having a possible T cell epitope. The synthesis and testing of those 27 peptides identified 18 binders. In view of this disclosure, the IPEA considers that the peptides identified in D5 can be seen as comprising "less than the full-length polypeptide sequence of native Tek" (they certainly comprise at least one residue of the native Tek if not a dipeptide), they can be seen as consisting "essentially" of one (or more) amino acid sequences which "represent" one or more of the Tek protein (according to the reference given on page 4 of the present application, they can be seen as "immaterial

variants" having the desired function) and they have been identified by their ability to bind to an MHC molecule and potentially stimulate an immune response. Thus, at least the subject matter of claims 1-7 and 12-14 is anticipated by said document (Articles 33 (2) and (3) PCT). Once the peptides have been identified, their production by recombinant methods, their use for obtaining antibodies as well as the pharmaceutical compositions and therapeutic/prophylactic methods do not seem to require any further inventive contribution from the skilled person. Thus, claims 8-11 and 15-41 do not fulfil the requirements of Article 33 (3) PCT.

vi) a similar disclosure is found in the documents M.P. Davenport et al., Immunogenetics 1995, Vol. 42, pages 392-397 (**D6**) and WO-97/41440 (**D7**), which are thus, considered to anticipate the same subject matter than D5 (claims 1-7 and 12-14 : Articles 33 (2) and (3) PCT; and claims 8-11 and 15-41 : Article 33 (3) PCT). In particular, D7 further refers to the production of the corresponding recombinant peptides and their use for producing an immune response (mono and polyclonal) antibodies as well as their relevance in therapeutic treatments. Thus, it further anticipates the subject matter of claims 15-30 and 33-41 (Articles 33 (2) and (3) PCT).

In view of the methods disclosed in D5-D7 and their general teachings (use of said methods for any known protein), the IPEA considers that once the Tek protein was known and available to the skilled person (as well as its potential therapeutical use in angiogenesis and tumorigenesis, see in particular D1 and D4), the mere use of these well-known methods for determining possible MHC binding peptides and/or potential T cell epitopes cannot amount to any inventive contribution. In other words, in the absence of any unexpected effect or advantageous property (such as the indicated selection of specifically-defined, purposefully-chosen epitopes with advantageous production of optimal vaccines which target tumour endothelia but not normal quiescent endothelia), the IPEA fails to see any inventiveness in the selection of specific peptides of the Tek protein and even less in the defined broad regions of the Tek receptor (whole Tek1 to Tek5 plus additional residues of the Tek protein) (Article 33 (3) PCT).

The attention of the Applicant is also drawn to the fact that the subject matter of claims 39-41 is directed to methods for treatment of the human or animal body and thus, it may be excluded from examination by Article 34(4)(a)(i) PCT in combination with Rule 67(iv) PCT too. Furthermore, for such a subject matter no unified criteria exist in PCT for the

assessment whether it is industrially applicable or not. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. Additional remarks to item VIII :

Article 6 PCT requires the claims to be "clear and concise", which is to say, according to the PCT Gazette, "PCT International Preliminary Examination Guidelines", 29.10.98, Section IV, III-4, the meaning of a claim has to be clear from the wording of the claim alone. Furthermore, according to **Rule 6.3 (a) PCT** "the definition of the matter for which protection is sought shall be in terms of the technical features of the invention", i.e. an independent claim should clearly specify **all** the essential (technical) features needed to define the invention and that, as a general rule, claims which attempt to define the invention, or a feature thereof, by a result to be achieved should be objected (PCT Gazette, "PCT International Preliminary Examination Guidelines", 29.10.98, Section IV, III-4.4 and 4.7). Thus, the following objections are raised under **Article 6 PCT** concerning the clarity of the claims:

i) the IPEA considers that the wording of claim 1 is ambiguous for the following reasons: (**i.a**) the reference to a "native Tek" without clearly given its specific SEQ ID No. does not fulfil the requirements of Article 6 PCT in combination with Rule 6.3 PCT which requires the claims to be drafted in terms of technical features. (**i.b**) the wording "comprises less than the full-length" is interpreted as comprising the full-length minus one or two residues. The IPEA fails to see a clear and unambiguous length definition in the wording "peptide" and/or "polypeptide", see for instance claims 2-3, 5 and 13 which define the native Tek as a "protein", whereas claims 16 and 19 define the wild-type Tek as a polypeptide. Page 4 in the description refers to a peptide as having "at least about 9 to 13" but without defining any upper limit. There is an explicit reference too on the same page to "less than 50% of the full-length" even if it also refers to general "fragments" without any further limitation. However, all these requirements are not found in the wording of the claims. (**i.c**) the wording "consists essentially" makes the actually scope of the claim ambiguous and open to any subjective interpretation. The reference on page 4 of the description does not

overcome this ambiguity. (**i.d**) the sentence "a sequence which represents an epitope" is also ambiguous. On page 4 it is said to comprise "immaterial variants" which are actually characterized by having only the desired function, i.e. any epitope having the same properties than the ones of the Tek epitope already "represents" a Tek epitope. (**i.e**) in view of the above cited ambiguities, claim 1 can be read as being directed to any peptide that "binds to an MHC molecule and stimulates an immune response", i.e. the claim is worded in terms of the result desired to be achieved, wherein, however the sentence "can bind" is also ambiguous as it does not clearly require that the peptide actually binds to an MHC molecule but that under certain conditions, not explicitly disclosed in the claims, it could bind to an MHC molecule. Thus, (**i.f**) any known peptide having the desired properties, namely the properties defined in (i.e), is seen as comprising less than the full-length of the native Tek protein (as it will certainly share at least one amino acid with the native Tek) and consisting "essentially" of one amino acid sequence "representing" at least one epitope of the Tek protein (with the same reasoning, it will certainly have at least one residue of said epitope) and thus, being novelty destroying.

ii) points (i.c), (i.d) and (i.e) apply for claims 2 , 3 and 4 (they do not refer to the SEQ ID No. of native Tek). Furthermore, in view of the word "essentially" the claimed peptides are not actually limited to the epitope(s) cited in these claims but they can be larger than said epitope(s) and thus, the objection (i.f) still applies for these claims too. For claims 4 and 5, the wording "substantially" makes their scope even more ambiguous (in this respect see PCT Gazette, "PCT International Preliminary Examination Guidelines", 29.10.98, Section IV, III-4.5a). In addition, the sentence "devoid of the sequence" is also ambiguous as (**ii.a**) there is no sequence disclosed in these claims and (**ii.b**) it is not clear whether the deletion of one residue is enough or else the whole sequence must be deleted.

iii) point (i.d) is valid for claim 6 too. In addition, (**iii.a**) the IPEA considers that a claim which refers to different sequence positions or locations (residue numbers) without giving any SEQ ID No. as a reference is unclear. In the present case, the reference to the sequence of Figure 1 overcomes this objection. However, the claim refers to an "equivalent" amino acid sequence region in a variant form of said Tek polypeptide without further defining said equivalence (location, structure, function, location and functional, etc... does "equivalence" mean to be exactly the same or else 95% identical, 90% ??) and the "variant" is only defined as having "substantially" (same, identical, similar, etc... 95%, 90%, etc...) functional "attributes". These attributes are, however, not defined in the claim and

a peptide can have many functions ("attributes"?) depending on its intended use, such as an enzymatic substrate, enzymatic inhibitor, immunogen, additive for foodstuff, etc.... On page 6 of the present application said "variant" is defined as being produced by insertion, deletion, addition or substitution of the native Tek polypeptide but without any further limitation and on page 7, the variants retaining the function are only said to be "preferred". However, on the same page 7 these variants are defined by a specific degree of identity. (**iii.b**) the Applicant is also reminded that "a sequence" can be as short as comprising only two residues, i.e. two residues appearing within the indicated sequences are already enough.

iv) the objections raised in respect of "variant form", "substantially" and "functional attributes" are relevant for the subject matter of claim 7 as well. In addition, the description clearly refers to peptide Z4 as not binding to HLA-A2 and peptide Z8 as showing a weak binding (Table 2, page 33). However, peptide Z8 is still comprised in the subject matter of claim 7.

v) claim 8 refers to an "stabilisation ratio" which actually depends on the assay conditions used (surface expression of HLA-A2 molecules on T2 cell line, incubation conditions of T2 cell line with peptides, concentration of the peptides, indirect immunofluorescence and analysis by flow cytometry, etc...). However, these conditions are not clearly specified in the claim. In addition, the scope of this claim is not supported in its whole breadth. In fact, the claim is "open-ended" so to say, "greater than 1.3" and thus, it embraces peptides having a "stabilisation ratio" of 10, 100, 1000 which do not have any support in the present description. These objections apply for the wording of claims 10 and 11 as well.

vi) the wording "substantially free" in claim 12 is open to subjective interpretation. In certain circumstances an ammonium sulfate precipitate of a crude homogenate could be seen as being "essentially free" of other material, whereas for other products and under other circumstances such a wording would imply a degree of purity of at least 90-95%. The sentence "naturally associated" is also ambiguous as far as "associated" implies the presence of other products linked to the claimed peptides or polypeptides (presence in the membrane??).

vii) the IPEA considers that claim 13 embraces (**vii.a**) short truncated Tek polypeptides (one residue, two residues shorter than the full-length, such as to fulfill the requirements

of claim 1) which have been arbitrarily mutated (such as to fulfil the requirements of claim 13, i.e. the presence of one sequence which is not characteristic of the native Tek protein) as well as (**vii.b**) short truncated Tek polypeptides fused with "tag" proteins (claim 14 would embrace products defined as in (vii.b)).

viii) the IPEA considers that the specificity of an antibody is not given by the method of production but by the particular epitope selected, i.e. an epitope which has a high homology to other known epitopes can certainly be used for raising epitope antibodies, however, it is not evident whether said antibodies will actually bind "specifically" to said epitope. Thus, claims 16-20 are not supported and are not enabling as far as these "specific" epitopes characteristic of the Tek polypeptide are not clearly identified in the wording of these claims.

ix) the IPEA considers that claim 21 embraces anything which presents the "epitope-specific binding activity" of the antibodies of claims 18-20 (wherein said "specificity" however is seen as being ambiguously defined, see point (viii) above). In particular, (**ix.a**) a "fragment" can be as short as consisting of a single residue. (**ix.b**) a derivative without any further limitation or restriction can be anything. By a suitable number and type (deletion, substitution, insertion) of modifications, any protein is "derivable" from the antibodies according to claims 18-20. (**ix.c**) the same objection applies for the wording "homologue" alone without any further indication of the specific degree of homology. (**ix.d**) a "functional equivalent" (and/or homologue) is also open to subjective interpretation as far as said function is not clear defined in the claim. In fact, any antibody can be seen as "functional homologue or equivalent" of any other antibody as far as they all produce a "(functional) homologous" immunoreaction. In addition, (**ix.e**) the word "equivalent" per se is also ambiguous (90%, 95%, 50%,etc...) (see also paragraph (iii) above).

x) the IPEA further considers that the method of claim 34 is not clearly defined. The regions TEK1 to TEK5 are not indicated in the claim. The conditions of hybridization are not disclosed. The hybridization alone is not enough for actually "obtaining" anything (in any case it only "identifies" something!), i.e. there are several steps missing in the claimed method for achieving the desired product.

regions in a variant form of said Tek polypeptide with substantially the same functional attributes.

7. A peptide according to any one of claims 1 to 6 which comprises one or more of the epitope sequences Z1, Z2, Z3, Z5, Z6, Z7, Z8, Z9, Z11, Z12 and Z32 as set forth in Tables 1 and 4, and/or one or more of a variant form of said "Z" epitope sequences with substantially the same functional attributes.

8. A peptide according to any one of the preceding claims which binds HLA-A2 with a stabilisation ratio of 1.3 or greater.

9. A peptide according to claim 8 which can stimulate T cell proliferation.

10. A peptide according to claim 8 or claim 9 which binds HLA-A2 with a stabilisation ratio of 1.5 or greater.

11. A peptide according to any one of claims 8 to 10 which binds HLA-A2 with a stabilisation ratio of 2.3.

12. A peptide according to any one of the preceding claims which is in an isolated and/or purified form, free or substantially free of material with which it is naturally associated.

13. A polypeptide which comprises a peptide according to any one of claims 1 to 12 and one or more amino acid sequences not characteristic of Tek protein.

14. A polypeptide according to claim 13 which is a

fusion protein.

15. The use of a peptide according to any one of claims 1 to 12 or of a polypeptide according to claim 13 or claim 14 in the formulation of a composition for use in prophylactic and/or therapeutic treatment.

16. The use of a peptide according to any one of claims 1 to 12 or of a polypeptide of claim 13 or claim 14 in the production of epitope-specific antibodies capable of reacting with epitopes of wild-type Tek polypeptide.

17. The use according to claim 16 wherein said antibodies are monoclonal antibodies.

18. An antibody capable of specifically binding to a peptide of any one of claims 1 to 12 or a polypeptide according to claim 13 or claim 14.

19. An antibody according to claim 18 which is capable of reacting with wild-type Tek polypeptide.

20. An antibody according to claims 18 or 19 which is a monoclonal antibody.

21. A fragment, derivative, functional equivalent or homologue of an antibody according to claim 18, claim 19 or claim 20, which retains the epitope-specific binding activity of said antibody.

22. A fragment according to claim 21 which comprises an Fab fragment consisting of VL, VH, Cl and CH1 domains; an Fd fragment consisting of VH and CH1 domains; an Fv fragment consisting of VL and VH domains of a single arm of an antibody; a dAb

36. A method of producing a peptide according to any one of claims 1 to 12 or a polypeptide according to claim 13 or claim 14 which includes the step of expressing a nucleic acid of claim 33 in an expression system.

37. A vector comprising a nucleic acid of claim 33.

38. A host cell containing a vector according to claim 37, or a construct, virus or plasmid according to claims 26, 27 or 28.

39. A method of therapeutic or prophylactic treatment of a patient, comprising administering an effective amount of a pharmaceutical composition of claim 31.

40. A method according to claim 39 comprising inoculating said patient at least three times with said pharmaceutical composition, the second inoculation being administered more than two weeks after the first inoculation.

41. A method of therapeutic or prophylactic treatment of a patient, which comprises introducing a sequence encoding a peptide according to any one of claims 1 to 12, or a polypeptide according to claim 13 or claim 14, into target host cells of the patient.

regions in a variant form of said Tek polypeptide with substantially the same functional attributes.

7. A peptide according to any one of claims 1 to 6 which comprises one or more of the epitope sequences Z1, Z2, Z3, Z4, Z5, Z6, Z7, Z8, Z9, Z11, Z12 and Z32 as set forth in Tables 1 and 4, and/or one or more of a variant form of said "Z" epitope sequences with substantially the same functional attributes.

8. A peptide according to any one of the preceding claims which binds HLA-A2 with a stabilisation ratio of 1.3 or greater.

9. A peptide according to claim 8 which can stimulate T cell proliferation.

10. A peptide according to claim 8 or claim 9 which binds HLA-A2 with a stabilisation ratio of 1.5 or greater.

11. A peptide according to any one of claims 8 to 10 which binds HLA-A2 with a stabilisation ratio of 2.3.

12. A peptide according to any one of the preceding claims which is in an isolated and/or purified form, free or substantially free of material with which it is naturally associated.

13. A polypeptide which comprises a peptide according to any one of claims 1 to 12 and one or more amino acid sequences not characteristic of Tek protein.

14. A polypeptide according to claim 13 which is a

fusion protein.

15. The use of a peptide according to any one of claims 1 to 12 or of a polypeptide according to claim 13 or claim 14 in the formulation of a composition for use in prophylactic and/or therapeutic treatment.

16. The use of a peptide according to any one of claims 1 to 12 or of a polypeptide of claim 13 or claim 14 in the production of epitope-specific antibodies capable of reacting with epitopes of wild-type Tek polypeptide.

17. The use according to claim 16 wherein said antibodies are monoclonal antibodies.

18. An antibody capable of specifically binding to a peptide of any one of claims 1 to 12 or a polypeptide according to claim 13 or claim 14.

19. An antibody according to claim 18 which is capable of reacting with wild-type Tek polypeptide.

20. An antibody according to claims 18 or 19 which is a monoclonal antibody.

21. A fragment, derivative, functional equivalent or homologue of an antibody according to claim 18, claim 19 or claim 20.

22. A fragment according to claim 21 which comprises an Fab fragment consisting of VL, VH, Cl and CH1 domains; an Fd fragment consisting of VH and CH1 domains; an Fv fragment consisting of VL and VH domains of a single arm of an antibody; a dAb

36. A method of producing a peptide according to any one of claims 1 to 12 or a polypeptide according to claim 13 or claim 14 which includes the step of expressing a nucleic acid of claim 33 in an expression system.

37. A vector comprising a nucleic acid of claim 33.

38. A vector according to claim 37 which is a plasmid.

39. A vector according to claim 37 which is a virus.

40. A host cell containing a vector according to claim 37, claim 38 or claim 39.

41. A method of therapeutic or prophylactic treatment of a patient, comprising administering an effective amount of a pharmaceutical composition of claim 31.

42. A method according to claim 41 comprising inoculating said patient at least three times with said pharmaceutical composition, the second inoculation being administered more than two weeks after the first inoculation.

43. A method of therapeutic or prophylactic treatment of a patient, which comprises introducing a sequence encoding a peptide according to any one of claims 1 to 12, or a polypeptide according to claim 13 or claim 14, into target host cells of the patient.